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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,224	SANDIG ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-53* is/are pending in the application.

4a) Of the above claim(s) *52 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 18-53 are currently pending.

Election/Restrictions

Applicant's election without traverse of Group I, claims 18-51, in the reply filed on 6/16/08 is acknowledged.

Applicant's election with traverse of various species, including "(a) replacing the gene coding for the Ig with a first functional sequence containing one or more RRSs and then integrating a second functional DNA sequence comprising a DNA sequence that codes for the target gene product into the functionalized precursor cell by use of a recombinase recognizing the RRSs"; "(e) a human hetero-hybridoma"; "(g) at a rearranged IgH locus"; "(n) ELISA"; "(r) frt"; "(y) secretion proteins"; "(i') antibodies"; and "(t') RRSs" in the reply filed on 6/16/08 is acknowledged. The traversal is on the ground(s) that the PCT Rules do not provide for election of species (Reply, page 5, paragraphs 4 and 5).

The PCT Administrative Instructions, Annex B, Part 1(f) indicate that a single claim that defines alternatives (i.e., a Markush claim) is governed by Rule 13.2 and that the requirements of Rule 13.2 pertaining to these claims are satisfied "when the alternatives are of a similar nature." Section (f) goes on to discuss the criteria by which alternatives are determined to be of a similar nature. Part 1(c) indicates that dependent claims avoid lack of unity considerations only if the independent claim is free of the prior art. Therefore, since the claims are currently free of the prior art, all species will be

examined. However, if the claims are amended such that prior art applies, the species election requirement may be imposed on the claims at that time.

Claims 52 and 53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/16/08.

Examination on the merits will commence at this time on claims 18-51 ONLY.

Priority

The status of the parent case(s) should be updated. The instant application is a national stage filing of PCT EP03/11027, which should be reflected in the first paragraph of the specification or in an application data sheet.

Claim Objections

Claim 33 is objected to because of the following informalities: It does not end with a period. Claim 38 is objected to because of the following informalities: The word "consisting" is misspelled at line 2. Claim 48 is objected to because of the following informalities: "DSM" is misspelled at line 1. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method of preparing a cell that expresses any target gene product such that it has an "essentially human" glycosylation pattern, said method including identifying a cell that is related to B lymphocytes and expresses immunoglobulin (Ig) that is not essential to the function of said cell; screening for some aspect of the locus of the Ig gene within said cell (in the interest of compact prosecution, step (b) has been interpreted as requiring identifying the location of an Ig gene within the genome of the cell; see the 35 U.S.C. § 112, second paragraph, rejection below); replacing the Ig gene with a first DNA sequence containing a recombinase recognition site (RRS); and then integrating a second DNA sequence containing the target gene product using a recombinase that recognizes the RRS in the first DNA sequence. In some dependent claims, the cell is a human heterohybridoma cell such as H-CB-P1 or PBG04 and the Ig gene is an IgH locus. In some dependent claims, the locus of the Ig gene provides an essentially human glycosylation pattern (presumably, for the target gene product). In some dependent claims, the RRS is frt and the recombinase is flp. In some dependent claims, the target gene product is an antibody. Some claims are drawn to the cell per se. One claim is drawn to a method of using the cell to produce the target gene product.

The specification in view of the art provides insufficient guidance for the skilled artisan to carry out the invention across its entire scope. Fussenegger (1999, *Trends in Biotechnology* 17: 35-42; reference A5 on IDS of 7/21/05) teaches that glycosylation is

a post-translational event for secreted proteins (page 40, column 1, paragraph 2 under section entitled "Glycosylation..."). Glycosylation occurs at particular amino acids in the endoplasmic reticulum and Golgi apparatus, where proteins are processed for secretion (ibid.); however, not all proteins are glycosylated. Except for claims 35, 39, and 47, the instant method is not limited to secreted proteins; therefore, the disclosure is not enabling for producing proteins that are not naturally glycosylated such that they possess an ”essentially human” glycosylation pattern, since there is no such pattern for these proteins.

Furthermore, Fussenegger teaches that glycosylation patterns are affected by many parameters, including the sequence of the polypeptide chain, the host cell and its set of glycosyltransferases and glycosidases, and the environment of the host cell (page 40, column 1, last paragraph). As discussed above, most of the instant claims place no limit on the amino acid sequence of the target gene product, so altering the sequence to change the glycosylation pattern of the product does not appear to be within the scope of this invention. Even if the scope of the product were narrowed to an antibody, the disclosure in view of the art would still fail to enable the entire invention. Yoo et al. (2002, *Journal of Immunological Methods* 261: 1-20; reference U) teach that around the time of the invention, it was known that different mouse and human hybridomas, myelomas, and hetero-hybridomas yield IgG chains with different glycosylation patterns (see section 5.4 at page 9). Specifically, Yoo teaches that mouse-human hetero-hybridomas add a particular glycan to IgG but mouse NSO myelomas and rat myelomas do not (ibid.). Regarding claim 22, which limits the cell to a hetero-hybridoma, and

claims 23, 44, 46, 48, and 49, which limit the cell to particular hetero-hybridoma lines, Yoo teaches that mouse-human hetero-hybridomas generally follow the glycosylation pattern characteristic of the mouse parental line (ibid.). The teachings of Yoo and Fussenegger indicate that around the time of the invention, selecting a cell that is capable of producing a given target gene product such that it has an "essentially human" glycosylation pattern would have constituted undue experimentation, since the glycosylation pattern imparted to a polypeptide by a given cell line was not predictable.

M.P.E.P. § 2164.03 reads, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. **In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.** See, *e.g., Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004)…In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be

required." As the above discussion illustrates, the glycosylation patterns imparted by at least a few B cell-derived cell lines on recombinant proteins were unpredictable at the time of the invention, so treatment of such diseases must be considered "nascent," and the amount of guidance required is relatively high.

Applicants present a single working embodiment in which a targeting vector including frt RRSs, "the place holder gene hobFc," and a gene encoding blasticidin (i.e., pVHCμCEShobFcblas) is transfected into H-CB-P1, a hetero-hybridoma cell, such that it is inserted at a rearranged Ig locus such that the Ig locus is replaced with the targeting vector, and yielding clone PBG04 (page 27, paragraph 2, through page 28, paragraph 3; page 16, last paragraph). PBG04 is then transfected with two vectors: one that expresses flp recombinase (pflp) and one that includes frt RRSs and a gene for GFP, green fluorescent protein (Example 4 at page 31, paragraph 2), resulting in green cells and indicating that recombination between the frt sequences occurred. At page 31, last paragraph et seq., applicants discuss "leptin Fc from PB604," but it is not clear whether this product is a natural product of PB604 or whether it is made using a particular targeting vector. The specification does not appear to include an example in which the claimed method is practiced.

While a singular, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill

in the art would not have a reasonable expectation of success in using the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 is drawn to a method for making a cell capable of "high yield expression" of a target gene product, but it is not clear which levels of expression is considered high and which are not. There is no basis provided in the claim for the relative term “high yield.” Clarification is required.

Claim 18 is drawn to a method for making a cell that expresses a product “having an essentially human glycosylation pattern,” but the scope of this limitation is not clear. First, it is not clear what constitutes a “human glycosylation pattern,” because the specification and art do not indicate that there is a particular pattern unique to humans. Furthermore, the scope of the limitation "essentially human" is unclear. Clarification is required.

Step (b) of claim 18 requires “screening for the locus of the Ig gene within the genome of the starting cell,” but the nature of this screening is not clear. Clarification is required. If step (b) is meant to disclose identifying the location of the Ig gene in the genome of the starting cell, the claim should recite such.

Step (d) of claim 18 requires integrating the second DNA sequence “by use of a recombinase," but this step does not particularly indicate any active steps by which the second DNA sequence is integrated. Clarification is required.

Because claims 2-23, 25, 27-41, and 43-51 depend from indefinite claim 18 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 27 refers to an immunoglobulin gene that is “a known locus,” but it is not clear which loci are known and which are not known. The claim does not indicate who or what is required to know of the locus. Clarification is required.

Claim 42 requires “screening for the locus of the Ig gene within the genome of the starting cell,” but the nature of this screening is not clear. Clarification is required. If step (b) is meant to disclose identifying the location of the Ig gene in the genome of the starting cell, the claim should recite such.

Claim 50 recites a cell whose light chain is inactivated or replaced; however, it is not clear which light chain is being referenced. Clarification is required.

Claim 51 is drawn to a method for expressing a gene product, but none of the steps necessarily results in this outcome. Clarification is required. The steps should match the scope of the preamble, i.e. they should necessarily result in the expression of a gene product.

No claims are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP

714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651